bluebird bio Presents Updated Data from Phase 2/3 Clinical Study of Lenti-D™ Gene Therapy for Cerebral Adrenoleukodystrophy (CALD) at the 13th European Pediatric Neurology Society (EPNS) Congress

Long-Term Follow-up Data Show That the 88% of Patients Treated in the Starbeam Study (ALD-102) Were Free of Major Functional Disabilities (MFDs) at Two Years, and Continued to Remain MFD-Free at up to Five Years of Follow-up

CAMBRIDGE, Mass.—(BUSINESS WIRE)—Sept. 18, 2019— bluebird bio, Inc. (Nasdaq: BLUE) today announced updated results from the clinical development program for its investigational Lenti-D™ gene therapy in patients with cerebral adrenoleukodystrophy (CALD) at the 13th European Pediatric Neurology Society (EPNS) Congress in Athens, Greece.[1,2]

CALD is a rare genetic and rapidly progressive disease that can lead to severe loss of neurologic function and death.[1,3,4] The Phase 2/3 Starbeam study (ALD-102) is assessing the efficacy and safety of Lenti-D in boys 17 years of age and under with CALD.[1] Updated data from the ongoing observational study (ALD-103) of allogeneic haematopoietic stem cell transplant (allo-HSCT) in boys 17 years of age and under with CALD were also presented.[2]

"With the longest follow-up from the Phase 2/3 Starbeam study now up to five years, the data show that all boys with CALD who were treated with Lenti-D and were free of major functional disabilities (MFDs) at 24 months continued to be MFD-free. Importantly, there were no reports of graft failure or treatment-related mortality, and adverse events were generally consistent with myeloablative conditioning," said David Davidson, M.D., chief medical officer, bluebird bio. "These results support the potential of Lenti-D as a treatment for CALD, which we hope may become an option for the boys and their families affected by this devastating disease."

Updated Results: Starbeam Study (ALD-102)

The Phase 2/3 Starbeam study has completed enrolment.[1] All reported data below are as of April 25, 2019 and reflect a total population of 32 patients with a median follow-up time of 21.2 months (0.0 – 60.2).[1] Of the 32 patients who have received Lenti-D as of April 25, 2019, 15 have completed study ALD-102 and enroled in a long-term follow-up study, 14 are currently on-study, and 3 are no longer on-study.[1]

The primary efficacy endpoint in the study is the proportion of patients who are alive and free of MFDs at Month 24.[1] MFDs are six severe disabilities commonly attributed to CALD and thought to have the most profound impact on a patient's ability to function independently, including loss of ability to communicate, cortical blindness, need for tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement.[5]

Of those patients who have or would have reached 24 months of follow-up and completed the study, 88 percent (N=15/17) continue to be alive and MFD-free in a long-term follow-up study.[1] The 14 patients currently on-study have less than 24 months of follow-up and have shown no evidence of MFDs.[1] The

longest follow-up of the additional 14 patients was 20.4 months.[1] Three out of the 32 treated patients did not or will not meet the primary efficacy endpoint; two patients withdrew from the study at investigator discretion, and one experienced rapid disease progression early on-study resulting in MFDs and death.[1]

Secondary and exploratory efficacy outcomes included: changes in neurologic function score (NFS), a 25-point score used to evaluate the severity of gross neurologic dysfunction by scoring across 15 symptoms in six categories; resolution of gadolinium enhancement (GdE), an indicator of active inflammation in the brain; and change in Loes score, an MRI measurement of white matter changes in CALD.[1] Of the 32 patients treated, 30 had stable NFS following treatment with Lenti-D, defined as NFS ≤4, without a change of >3 from baseline.[1] Loes score generally stabilised within 12-24 months and GdE+ enhancement resolved in most patients following Lenti-D treatment.[1]

The primary safety endpoint is the proportion of patients who experience acute (≥Grade 2) or chronic graft-versus-host disease (GvHD) by Month 24.[1] GvHD is a condition that may occur after an allo-HSCT where the donated cells view the recipient's body as foreign and attack the body.[6] No events of acute or chronic GvHD have been reported post-Lenti-D treatment and there have been no reports of graft failure, cases of insertional oncogenesis, or replication competent lentivirus.[1] The safety profile of Lenti-D is generally consistent with myeloablative conditioning with busulfan and cyclophosphamide, the standard preparative regimen completed prior to HCST.[1] Three adverse events (AE) have been deemed potentially related to treatment with Lenti-D and include BK-mediated viral cystitis (N=1, grade 3) and vomiting (N=2, grade 1); all three resolved using standard measures.[1]

"I see the impact CALD has on my young patients and their families in my practice and understand the urgent need for additional treatment options," said Caroline Sevin, M.D., Paediatric Neurology Department, Hôpital Bicêtre-Hôpitaux Universitaires Paris Sud, Le Kremlin Bicêtre, France, and an investigator in the Starbeam study. "These updated data from the Starbeam study are encouraging because there continues to be no report of graft-versus-host disease or graft failure post-Lenti-D treatment, and Lenti-D utilises a child's own cells eliminating the need for a donor as well as complications that may be involved with donor cells."

Updated Results: ALD-103 Study

Allo-HSCT has been successfully used to treat CALD but comes with risks, including graft failure, acute and chronic GvHD, and death, as well as infection as a result of the immune suppression required post-transplant.[5-10] The ongoing observational study ALD-103 is designed to assess safety and efficacy outcomes of this treatment option in boys 17 years of age or younger with CALD.[2] The study measures CALD disease-related outcomes in four patient cohorts: Early disease 1 (N=21; Loes ≤4 and NFS ≤1); Early disease 2 (N=9; Loes >4 to 9 and NFS ≤1); All early disease (N=30; Loes ≤9 and NFS ≤1); and Advanced disease (N=10; Loes >9 OR NFS >1). Transplant-related outcomes are assessed by donor stem cell source and by conditioning regimen.[2]

As of February 11, 2019, 47 patients who had undergone allo-HSCT were enroled in the ALD-103 study.[2] Updated results showed early treatment with allo-HSCT provides improved overall and MFD-free survival for patients with CALD irrespective of the stage of early disease.[2] In the all early disease cohort

at 24 months post-allo-HSCT, 77.2 percent of patients achieved MFD-free survival and 89.1 percent achieved overall survival compared to 35.0 percent and 52.5 percent, respectively, in the advanced disease cohort at 24 months post-allo-HSCT.[2]

The risk associated with allo-HCST varied by donor source.[2] While there were no substantial differences observed between the groups in ALD-103, more patients who were treated with umbilical cord stem cells from an unrelated donor (38.9 percent [7/18]) experienced engraftment failure by Month 24 compared to patients who received bone marrow or umbilical cord cells from a matched sibling donor or bone marrow cells from an unrelated donor (0 percent in both groups).[2]

Analyses done by conditioning regimen showed higher rates of acute (42.9 percent [6/14]) and chronic (54.5 percent [6/11]) GvHD in patients who received myeloablative conditioning with busulfan and cyclophosphamide compared to those who were myeloablated with busulfan and fludarabine (6.3 percent [1/16] and 13.3 percent [2/15], respectively).[2]

In total, 23.5 percent (8/34) and 27.6 percent (8/29) of patients enroled in the study experienced acute and chronic GvHD, respectively.[2] The overall rates of 100-day and 1-year transplant-related mortality were 0 percent (0/38) and 12.1 percent (4/33), respectively.[2] The overall rate of engraftment failure by Month 24 was 21.6 percent occurring in 8 of 37 evaluable patients.[2] Analyses also showed higher rates of engraftment failure in patients who received myeloablative conditioning with busulfan and fludarabine, 28.6 percent (6/21) experienced engraftment failure by 24 months compared to 0 percent in the busulfan and cyclophosphamide group.

These data suggest that, while allo-HSCT appears to halt disease progression in early disease, it can be associated with serious safety risks and most transplant-related risks vary by donor source and conditioning regimen.[2]

Oral Presentations at EPNS

Phase 2/3 Trial to Address the Safety and Efficacy of Lenti-D Hematopoietic Stem Cell Gene Therapy for Cerebral Adrenoleukodystrophy

Presenter: Dr. Caroline Sevin, Hôpital Universitaire Bicêtre-Paris Sud, Paris, France
Date & Time (Parallel Session 2D: Neurometabolic Disorders I): Wednesday, September 18, 2019, 4:30 – 6:15 p.m. GMT+3 (9:30 – 11:15 a.m. EDT)

An observational study of outcomes of Allogeneic Hematopoietic Stem Cell Transplant in patients with Cerebral Adrenoleukodystrophy (CALD)

Presenter: Dr. Florian Eichler, Center for Rare Neurological Diseases, Associate Professor of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, USA
Date & Time (Parallel Session 2D: Neurometabolic Disorders I): Wednesday, September 18, 2019, 4:30 – 6:15 p.m. GMT+3 (9:30 – 11:15 a.m. EDT)

Additional Information About the Clinical Development Program for Lenti-D
bluebird bio is currently enroling patients for a Phase 3 study (ALD-104) designed to assess the efficacy and safety of Lenti-D after myeloablative conditioning using busulfan and fludarabine in patients with CALD. Contact clinicaltrials@bluebirdbio.com for more information and a list of study sites.

Additionally, bluebird bio is conducting a long-term safety and efficacy follow-up study (LTF-304) for patients who have participated in bluebird bio-sponsored studies of Lenti-D for CALD.

For more information about the Phase 2/3 Starbeam study visit:
https://clinicaltrials.gov/ct2/show/NCT01896102

The European Medicines Agency (EMA) accepted Lenti-D gene therapy for the treatment of CALD into its Priorities Medicines scheme (PRIME) in July 2018, and previously granted Orphan Medicinal Product designation to Lenti-D.

The U.S. Food and Drug Administration (FDA) granted Lenti-D Orphan Drug status, Rare Paediatric Disease designation, and Breakthrough Therapy designation for the treatment of CALD.

About Cerebral Adrenoleukodystrophy
Adrenoleukodystrophy (ALD) is a rare, X-linked metabolic disorder that is estimated to affect one in 21,000 male newborns worldwide.[4,11] ALD is caused by mutations in the *ABCD1* gene that affect the production of adrenoleukodystrophy protein (ALDP) and subsequently cause toxic accumulation of very long-chain fatty acids (VLCFAs) primarily in the adrenal cortex and white matter of the brain and spinal cord.[3,4]

Approximately 35-40 percent of boys with ALD will develop CALD, the most severe form of ALD.[5,12] CALD is a progressive neurogenerative disease that involves breakdown of myelin, the protective sheath of the nerve cells in the brain that are responsible for thinking and muscle control.[5,13-15] Symptoms of CALD usually occur in early childhood and progress rapidly, if untreated, leading to severe loss of neurologic function, and eventual death, in most patients.[5,13-15]

Currently, the only therapeutic option for patients with CALD is allo-HSCT.[5,8,9] Beneficial effects have been reported if allo-HSCT is performed early in the course of cerebral disease.[5,7-10] Potential complications of allo-HSCT, which can be fatal, include graft failure and rejection, GvHD, and opportunistic infections, particularly in patients who do not have an HLA-matched sibling donor for transplant.[5,8,9]

Early diagnosis of CALD is important, as the outcome of treatment varies with the clinical stage of the disease at the time of transplant.[5,7-10,14] Newborn screening for ALD is a critical enabler of early diagnosis and successful treatment of ALD.[4,14,16-18] In the United States (U.S.), newborn screening for ALD was added to the Recommended Universal Screening Panel in February 2016 but is currently active in only a limited number of states.[17,19-21] Outside the U.S., the Minister of Health in the Netherlands has approved the addition of adrenoleukodystrophy to the newborn screening program, and a pilot started in 2019. [21]

About bluebird bio, Inc.
bluebird bio is pioneering gene therapy with purpose. From our Cambridge, Mass., headquarters, we're developing gene therapies for severe genetic diseases and cancer, with the goal that people facing potentially fatal conditions with limited treatment options can live their lives fully. Beyond our labs, we're working to positively disrupt the healthcare system to create access, transparency and education so that gene therapy can become available to all those who can benefit.

bluebird bio is a human company powered by human stories. We're putting our care and expertise to work across a spectrum of disorders by researching cerebral adrenoleukodystrophy, sickle cell disease, transfusion-dependent β-thalassaemia and multiple myeloma using three gene therapy technologies: gene addition, cell therapy and (megaTAL-enabled) gene editing.

bluebird bio has additional nests in Seattle, Wash.; Durham, N.C.; Zug, Switzerland; Munich, Germany; Milan, Italy; Utrecht, the Netherlands; Hampshire, United Kingdom; and Paris, France.

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Forward-Looking Statements
This release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the clinical development and commercial potential of the Company's Lenti-D product candidate to treat cerebral adrenoleukodystrophy. Any forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, risks that the efficacy and safety results for our Lenti-D product candidate from the Starbeam Study seen to date will not continue or persist, the risk of cessation or delay of any of the ongoing clinical studies and/or our development of Lenti-D, the risks regarding future potential regulatory approvals of Lenti-D, including the risk that the Starbeam Study will be insufficient to support regulatory submissions or marketing approval in the U.S. and EU, and the risk that any one or more of our product candidates will not be successfully developed, approved or commercialised. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our most recent Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and bluebird bio undertakes no duty to update this information unless required by law.

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References

1. Sevin C, Eichler F, Duncan C, *et al.* Phase 2/3 Trial to Assess the Safety and Efficacy of Lenti-D Hematopoietic Stem Cell Gene Therapy for Cerebral Adrenoleukodystrophy. Oral presentation (Abstract #OC036). 13th European Pediatric Neurology Society (EPNS) Congress; 2019 Sep 17-21; Athens, Greece.
2. Eichler F, Boelens JJ, Chiesa R, *et al.* An observational study of outcomes of Allogeneic Hematopoietic Stem Cell Transplant in patients with Cerebral Adrenoleukodystrophy (CALD). Oral presentation (Abstract #OC039). 13th European Pediatric Neurology Society (EPNS) Congress; 2019 Sep 17-21; Athens, Greece.
3. Moser HW. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. *Brain*. 1997;120(Pt 8):1485-508.
4. Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. *Nature Clin Pract Neurol.* 2007;3(3):140-51.
5. Raymond GV, Aubourg P, Paker A*, et al*. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy With and Without Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant.* 2019; 25: 538-48.
6. Jaing, TH. Complications of haematopoietic stem cell transplantation. *ISBT Science Series.* 2011;6:332–336.
7. Mahmood A, Raymond GV, Dubey P, et al. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: a comparison study. *Lancet Neurol.* 2007;6(8):687-2.
8. Miller WP, Rothman SM, Nascene D, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. *Blood.* 2011;118(7):1971-8.
9. Peters C, Charnas LR, Tan Y, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. *Blood*. 2004;104(3):881-8.
10. Polgreen LE, Chahla S, Miller W, et al. Early diagnosis of cerebral X-linked adrenoleukodystrophy in boys with Addison's disease improves survival and neurological outcomes. *Eur J Pediatr.* 2011;170(8):1049-54.
11. Bezman L, Moser A, Raymond G. Adrenoleukodystrophy: Incidence, New Mutation Rate, and Results of Extended Family Screening. *Ann Neurol* 2001;49:512–517.
12. Kanakis G and Kaltsas G. Adrenal Insufficiency Due to X-Linked Adrenoleukodystrophy. *NCBI*. 2018.
13. Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet J Rare Dis.* 2012;7:51.
14. Mahmood A, Dubey P, Moser HW, et al. X-linked adrenoleukodystrophy: therapeutic approaches to distinct phenotypes. *Pediatr Transplant*. 2005;9 Suppl 7:55-62.
15. Suzuki Y, Takemoto Y, Shimozawa N, et al. Natural history of X-linked adrenoleukodystrophy in Japan. *Brain Dev*. 2005;27:353-7.
16. Taylor JL, Lee S. Lessons learned from newborn screening in pilot studies. *N C Med J.* 2019;80:54-8.
17. Moser AB, Fatemi A. Newborn screening and emerging therapies for X-linked adrenoleukodystrphy. *JAMA Neurol*. 2018;75:1175-6.
18. Wiens K, Berry SA, Choi H, et al. A report on state-wide implementation of newborn screening for X-linked adrenoleukodystrophy. *Am J Med Genet A*. 2019;179(7):1205-13.
19. Kemper AR, Brosco J, Comeau AM. Newborn screening for X-linked adrenoleukodystrophy: evidence summary and advisory committee recommendation. *Genet Med.* 2017;19(1):121-6.
20. Hubbard WC, Moser AB, Liu AC, et al. Newborn screening for X-linked adrenoleukodystrophy (X-ALD): validation of a combined liquid chromatography-tandem mass spectrometric (LC-MS/MS) method. *Mol Genet Metab.* 2009;97(3):212-20.
21. Salzman R, Kemp S. ALD Info: Newborn Screening. Available from: https://adrenoleukodystrophy.info/clinical-diagnosis/newborn-screening. Last accessed 12 September 2019.